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and an acceleration of the synthesis and release of glucose from the liver.
Endocrine responses which influence these metabolic changes include an
enhanced secretion of both insulin and glucagon from pancreatic islet (continued)

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cells and a resultant decrease in the molar ratio of insulin to glucagon in plasma. The secretion of the adrenal glucocorticoids and growth hormone are increased as may be the secretion of catecholamines.

The accelerated release of glucose from the liver is generally accompanied by an increase in the glucose pool size and an increase in the rate of glucose utilization as a cellular fuel. This is especially true for the phagocytic cells during pyogenic infections. The increased utilization of amino acids as a substrate for hepatic gluconeogenesis provides the excess amino nitrogen groups used by the liver for ureagenesis which is also accelerated when acute infection develops in a normally nourished host.

The hormonal, enzymatic, and substrate interrelationships within the liver combine in their effects to inhibit ketogenesis and stimulate hepatic lipogenesis during acute sepsis.

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An invited paper for presentation by Dr. Beisel at a symposium entitled

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New research findings are helping to clarify the complex interrelationships among various metabolic pathways and molecular mechanisms used by host cells during their responses to generalized infections. These responses are required to supply the demands for increased quantities of energy-generating substrates that body cells must have during periods of fever, stress, and tissue repair. We need to learn more about the basic mechanisms which account for stimulated gluconeogenesis and ureagenesis with concomitant inhibition of "starvation ketogenesis" during sepsis.

Even with the presently available data, it remains difficult to identify the true relationships among key, interacting host metabolic factors during sepsis. These include the availability, redistribution and utilization rates of various energy-yielding substrates, hormonal effects, and the responsiveness of different host cells. Many published studies have failed to control or include data on variables now known to be of major importance. Since starvation or semistarvation is a major variable in sepsis-related metabolic responses, it is necessary that control observations be obtained in appropriately matched "pair-fed" groups. Many metabolic responses exhibit a biphasic pattern during the course of a septic process; it is therefore important that a longitudinal series of measurements be obtained, or at a minimum, that changes observed early in a disease not be lumped together with late ones. Measurements made during the agonal moments of a disease process are especially difficult to interpret.

Since the concentrations of any substance measured in a body "pool" represent the algebraic summation of all existing effects on both its input and outflow rates from the pool, it is important that these latter types of kinetic data be obtained whenever changes in concentration are observed. Host metabolic responses are influenced by the dose, virulence, and species of invading microorganism, so it is helpful to gather and publish data on these variables also. Resistance factors such as the preexisting immunological and nutritional states of the host are similarly valuable.

Historical Aspects

This brief review of gluconeogenesis, ureagenesis, and ketogenesis during sepsis is, in fact, an assessment of energy-generating mechanisms in host tissues. The importance of meeting energy needs of the body to help in the medical management of febrile infections and other severe stresses is now receiving widespread attention, although, as shown in Table 1,[1,2] the concept is not a new one. In the 1830's, Graves began teaching about the importance of giving food to patients with febrile illnesses, as did von Hosslin in 1882. Voit in 1895 first showed the nitrogen-sparing action of carbohydrate in dogs with experimental endotoxin fevers, and, in 1909, studies by Shaffer and Coleman demonstrated a similar protein-sparing effect of carbohydrate feedings during typhoid fever. Dietary therapy then became widely used for treating some infections, especially chronic ones, such as tuberculosis.

In more recent years, detailed information has been generated at the molecular level about the occurrence, scope, and role of the many

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interacting biochemical, hormonal, and nutritional changes which characterize the host response to an acute generalized infectious disease.[3] This brief review will focus upon three closely interwoven aspects of the energy generating mechanisms: gluconeogenesis, ketogenesis, and ureagenesis.

Gluconeogenesis

It has long been taught that insulinopenic "juvenile" diabetic patients spill sugar in the urine and require extra amounts of insulin if they develop a febrile infection.[4] This increased need for insulin has been interpreted, for many decades, as a sign of transient insulin resistance induced by the infection. However, in a recent review, Long[5] showed that the production of glucose is accelerated in patients with sepsis. The increase in glucose production during surgical sepsis is so great that it may not be inhibited by infusions of 5% dextrose.[6] Studies in laboratory animals have confirmed the occurrence of accelerated gluconeogenesis and glycolysis in the liver.[7-10] As illustrated schematically in Figure 1, gluconeogenesis is accelerated during sepsis by the stimulatory action of several hormones on enzymes involved in glucose synthesis and/or by the increased availability within the liver of the necessary gluconeogenic substrates. Although the kidneys can also manufacture glucose, little is known about their possible contribution to blood glucose values in an infected host.

A major difference in hormonal influences during sepsis is the usual increase in insulin secretion, in contrast to the decreased output of insulin, which is typical of adaptation to simple starvation.

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Despite the frequent presence of higher insulin concentrations in plasma during sepsis,[11-15] glucagon secretion is increased[10,13-17] with a resulting decrease in the insulin/glucagon ratio. In addition to an increased pancreatic secretion of glucagon, the catecholamines may also be secreted in excess, especially during gram-negative sepsis.[18-20] Both glucagon and the catecholamines stimulate the accelerated hepatic production and release of glucose by their ability to activate hepatic adenylate cyclase. There is also an increase during most acute infections in the production of the adrenal glucocorticoids[18,21] and growth hormone.[22,23]

During sepsis, the liver uses all of its usual substrates for producing glucose. These include lactate, pyruvate, glycerol, alanine, and other gluconeogenic amino acids, but the utilization ratio among these substrates changes. The increase in gluconeogenesis can be accounted for, in part, by the utilization of alanine derived from skeletal muscle protein.[5-9,20,24-25] In addition, lactate is also released in increased amounts from muscle[27-29] and areas of inflammation during sepsis and is then used for gluconeogenesis. The carbons from lactate contribute only to the recycling of glucose, while alanine could contribute carbon from the amino acids to replace the glucose lost by oxidation.[7]

Evidence to support these statements has been obtained by a series of definitive studies emerging from several different laboratories. The group led by Kinney[5,6,25,30] measured CO_2 in expired air, O_2 uptake, caloric intake, and nitrogen balance in patients with surgical sepsis

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in order to calculate resting metabolic expenditures and energy balances.
The combined stresses of trauma and infection caused consistently negative
balances of nitrogen and energy. By measuring $^{14}CO_2$ in expired air after
[^{14}C]glucose administration, Long et al[6] showed a 3-fold increase in the
pool size, turnover rate, and oxidation rate of glucose in patients with
major injury and sepsis (see Table 2). Further, the carbohydrate pool
model used by Long[5] suggested that the conversion of glucose carbon
into fat was accelerated in septic patients. An increase in lipogenesis
was also suggested in septic patients on the basis of their greater
increase in respiratory quotient values while receiving glucose in
contrast to the values observed in normal control subjects.

The contribution of alanine to the accelerated gluconeogenesis
was confirmed in septic patients[5,6] by means of radioactively labeled
alanine (see Table 2). This use of alanine as a substrate for
gluconeogenesis was shown to remain increased despite the fact that
the patients were being infused with exogenous glucose at normal hepatic
glucose production rates. Thus, gluconeogenesis from alanine was not
suppressed during sepsis, as was observed in normal subjects during an
infusion of 5% glucose solution. It was found, in addition, that the
oxidation of alanine in septic patients was equivalent to that observed
in normal subjects.

Observations by Imamura et al[28] and O'Donnell et al[29] suggested
that an accelerated metabolism of branched-chain amino acids in
peripheral tissues of patients with sepsis was contributing

importantly to an increased in vivo synthesis of alanine. The newly formed alanine could then be used to provide additional substrate for hepatic gluconeogenesis.

In ongoing studies performed in rhesus monkeys during non-lethal pneumococcal sepsis, Wannemacher et al[8,9] found that the production of glucose increased from 7.2 to 11.4 mg/min/kg while its utilization rate increased from 7.3 to 11.5 mg/min/kg. At the same time, the endogenous synthesis of alanine increased from 0.53 to 0.60 mmol/hr/kg while its utilization rate increased from 0.53 to 0.87 mmol/hr/kg. During sepsis, the use of newly synthesized alanine for gluconeogenesis jumped from 38 to 77%. Similarly, in the acute stages of pneumococcal sepsis in the rat, the rate of glucose synthesis, as measured by isotope dilution of $2-[^3H]$glucose, was almost twice that observed in control rats.[8] The rate of increase in glucose synthesis seemed to correlate with the availability of sufficient substrate rather than with the gluconeogenic capacity of the liver.

Alanine and glutamine are quantitatively the major amino acids released from skeletal muscle. The total amounts of these amino acids released during either fasting or sepsis are far greater than can be accounted for by the proteolysis of muscle proteins. This excess release can be explained by the synthesis of alanine and glutamine in skeletal muscle using nitrogen groups derived from the oxidation of the branched-chain amino acids and carbon from pyruvate or other amino acids. Glutamine can enter the liver to be used for gluconeogenesis,

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it can enter the kidney for production of ammonia, or it can be taken up by intestinal mucosa cells and converted into alanine.

Body cells respond differently in their ability to utilize glucose during periods of sepsis. Skeletal muscle can utilize available glucose,[9,32] ketone bodies,[33,34] and branched-chain amino acids[29] as substrates for energy, but the use of free fatty acids may diminish.[29] However, an increased output of lactate from muscle indicates that the rate of aerobic glycolysis may be proportinately reduced. At the same time, the availability of ketones is reduced. As a net result, an accelerated catabolism of skeletal muscle protein appears to be the principal mechanism used by the body during acute febrile illnesses to obtain free branched-chain amino acids which can be used as sources of energy. This process, in turn, contributes to the enhanced production of alanine.

Quite a different pattern of glucose utilization is taking place in neutrophils and other phagocytic cells. It is well established that phagocytic activity is accompanied by a burst of oxidative activity via the pentose phosphate pathway.[1,4] In rats studied during both the acute and agonal stages of pneumococcal sepsis,[7,8] the rate of recycling of glucose was found to be slightly but significantly increased when measured using glucose with a uniform $[^{14}C]$ tag as compared to $2-[^{3}H]$glucose.

This observation was studied in greater detail using glucose labeled at either the 1st or 6th carbon atoms. The oxidation of the glucose labeled on the 1st carbon was accelerated, while no change was

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observed in the rate of $^{14}CO_2$ production from glucose labeled in the 6th carbon. Thus, this difference indicated that the rate of glucose oxidation via the pentose phosphate pathway was greater during the agonal stages of infection than during the acute stages. Since the acceleration in rates of glucose oxidation seemed to follow the severity of bacteremia, the increase in pentose phosphate pathway oxidation of glucose could best be accounted for by a massive increase in phagocytic activity of white blood cells.[8]

Failure of Gluconeogenesis

While an infection-induced acceleration of gluconeogenesis is characteristic of the early periods of fever, the synthesis of glucose may not be sustained if the infection becomes overwhelmingly severe. The terminal hours of a lethal infection (or experimental endotoxemia) in laboratory rodents and subhuman primates is often characterized by plummeting body temperatures and the virtual disappearance of glucose from blood and of stored glycogen from tissues.[35-38] The combination of severe terminal hypothermia and hypoglycemia implies that the mechanisms for producing energy-yielding substrates have been strongly curtailed in the dying animal.

Many mechanistic studies have been performed in an attempt to identify specific defects in enzyme activities or metabolic pathways that could account for the terminal failure of gluconeogenesis. Most of these studies have produced "negative" data. The electron transport system in mitochondria remains intact, the TCA cycle remains operative,

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oxidative phosphorylation may be reduced somewhat but is not uncoupled and no enzyme system becomes entirely non-functional,[33,39] However, an agonal breakdown of carbohydrate production by the liver has been documented during experimentally induced endotoxemia.[37,38] This can be partially prevented by the prophylactic administration of glucocorticoid hormones in pharmacological doses. This observation led Berry and his coworkers to postulate almost two decades ago that the ability of adrenal glucocorticoids to induce certain key liver enzymes might account for the beneficial role of these steroids in experimental endotoxemia.[37,38]

A subsequent search for hepatic enzyme defects during infection has led to the findings of at least two changes that could interfere with hepatic gluconeogenesis. Decreased activity of glucose-6-phosphatase has been detected during pneumococcal sepsis in rabbits.[39] In studies performed during pneumococcal sepsis in rats, Canonico et al[41,42] detected a decline in the activity of several enzymes localized within the endoplasmic reticulum including glucose-6-phosphatase. The decline in the enzyme could contribute to an agonal stage decline in the gluconeogenic capacity of the liver.

More importantly, in the agonal stages of pneumococcal sepsis in rats[40] or during Salmonella endotoxemia[44] in mice, there is a reduction of phosphoenolpyruvate carboxykinase (PEPCK) activity. This is a key, rate-limiting enzyme used to permit glucose to be synthesized from pyruvate or lactate. PEPCK serves to regulate the phosphorylation of oxaloacetic acid and thus allows carbon-containing molecules from

the Krebs cycle to enter into the Embden-Myerhoff pathway, and eventually into glucose. PEPCK is one of the enzymes whose activity may be induced by corticoid hormones as well as by glucagon. Berry has observed the release into the serum of endotoxemic mice of an endogenous factor (possibly released by macrophages or T-cells) which could inhibit PEPCK activity.[45]

Data obtained from in vitro systems do not necessarily prove that changes in hepatic enzyme activities are responsible for the terminal hypoglycemia observed in vivo. The data concerning a terminal decline of gluconeogenesis are certainly valid during lethal endotoxemic shock in experimental animals, but are less conclusive during in vivo infections due to microorganisms that fail to release any lipopolysaccharide endotoxin.

The clinical appearance of hypoglycemia during sepsis in human patients can generally be explained on the basis of either substrate exhaustion or direct hepatocyte injury. The hypoglycemia commonly encountered during sepsis in neonatal infants[46] and sometimes in protein-depleted adult patients serves as a clinical illustration of substrate depletion, during which the ability of the body to generate or release substrate molecules no longer can keep up with the needs for glucose production. On the other hand, hypoglycemia during severe viral hepatitis[47] or yellow fever[35] can probably best be explained by direct virus-induced cellular injury or necrosis throughout the liver.

Acute infections characteristically initiate a sizable loss of body nitrogen if they occur in well-nourished young adults.[1,3,4] In contrast, negative nitrogen balances associated with an acute infection are only minimal in elderly, chronically ill, or malnourished populations, or in obese subjects who have become adapted to a regimen of semistarvation.[48-50] After a marked initial loss of total body nitrogen, patients who experience a chronic infection enter into a state of relative nitrogen balance equilibrium despite their cachectic appearance. Similarly, neonatal infants possess very little muscle mass or protein reserves at the time of birth. Clinical experiences in these kinds of patients suggest that after readily mobilized stores of body protein become depleted, little additional protein can be degraded for purposes of gluconeogenesis without disrupting essential body functions. A continued depletion of body protein stores for use in gluconeogenesis and ureagenesis would compromise the remaining defense mechanisms that continue to be important in resistance against infection, wound healing, and visceral organ functions. Protein-depleted patients are thus "at risk" from hypoglycemia during any severe infection.

Wilmore[2] has called attention to other problems in glucose metabolism in burned patients who develop bacterial sepsis. Severely burned patients with sepsis exhibited an increased glucose space and an intermediate rate of glucose utilization, but their glucose disappearance rates and insulinogenic indices were below values found in normal control subjects. Further, alanine infusions failed to

increase glucose concentrations in septic, burned patients as they did in nonseptic patients with comparable burn injuries; the septic patients showed higher baseline concentrations of gluconeogenic amino acids in plasma than did burn patients without sepsis. These types of severely burned patients with gram-negative sepsis would thus seem to be exhibiting some degree of functional failure in their hepatic gluconeogenic capacity. This group may represent, in man, the type of defect in gluconeogenesis exhibited by endotoxemic mice.[44]

Ureagenesis

The increased utilization of body proteins as substrates for the synthesis of glucose could account for the continuing (or increased) losses of urinary nitrogen observed during infectious diseases. Metabolic balance studies performed in a number of different kinds of infections showed a consistently negative nitrogen balance beginning, in most instances, soon after the onset of fever.[3,4] Negative nitrogen balances could be ascribed, in part, to anorexia and a reduction in dietary nitrogen intake.[3,4] The major factor, however, was a continuing loss of urinary nitrogen during infection-induced anorexia in contrast to a progressively diminished nitrogen loss which is typically seen during simple starvation. Urea is the predominant component in the loss of urinary nitrogen in studies performed during infections in man and in monkeys. This urea is synthesized primarily by the liver.

During accelerated gluconeogenesis, the amino group of alanine contributes importantly to the synthesis of urea. The increase in

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ureagenesis during infection would not seem to require any changes in the enzymatic machinery normally used for this purpose. Rather, the increased utilization of amino acids as substrates for gluconeogenesis is sufficiently large so that the amino nitrogen generated from transamination reactions in the liver can account for almost 100% of the infection-related increase in urea excretion.[9] Some of the excess amino nitrogen is excreted as ammonia and contributes to the urinary loss of total nitrogen in febrile illnesses.[3,4]

Based on the information available from studies using radioactively tagged alanine, one must conclude that the accelerated ureagenesis seen during generalized infection is driven by the extra amount of amino nitrogen, a substrate which becomes available within the liver as the final consequence of a long series of metabolic responses to infection which include: 1) accelerated proteolysis within muscle and other somatic tissues; 2) increased production of alanine from branched-chain amino acids in muscle; 3) increased release of alanine from muscle; 4) accelerated hepatic uptake of amino acids from plasma; and 5) accelerated hepatic gluconeogenesis from amino acid substrates.

The entry of ammonia into the urea cycle within the liver leads initially to the formation of carbamylphosphate which reacts with ornithine to form citrulline. Aspartic acid supplies the second nitrogen atom of urea by reacting with citrulline to form argininosuccinate; this, in turn, splits into fumarate and arginine. Urea is generated from the splitting of arginine into ornithine and urea. Aspartic acid

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is generated by the transfer of ammonia or amino groups via transamination reactions to glutamate and aspartic acid. Approximately 35 to 40 kcal are required for the synthesis of one mole of urea. Thus, the use of amino acid substrates for gluconeogenesis consumes more energy than does the use of lactate as a substrate. On a molar basis, amino acids will supply 20% less energy than the equivalent amount of glucose. Therefore, the expenditure of body protein as an energy source is a relatively inefficient process. In contrast, body fat is a far more efficient source of energy.

Ketogenesis

Under conditions of simple starvation, hepatic ketogenesis is thought to follow an increased mobilization of free fatty acids (FFA) from peripheral adipose depots and their accelerated transport into liver. Mobilization of FFA is coupled with an enhanced hepatic capability for synthesizing ketones. A starvation-induced decline in plasma insulin concentrations can help account for the mobilization of FFA. At the same time, an increase in plasma glucagon and the glucagon/insulin molar ratio appears to stimulate hepatic ketogenesis.

Although some degree of starvation is generally present during sepsis, the hormonal responses and availability of substrates are different during sepsis from those which characterize simple starvation. In attempting to identify the mechanisms which prevent (or reverse) starvation-induced ketosis during sepsis, it is first necessary to consider the wide spectrum of changes which occur in the metabolism

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of FFA.. These are illustrated schematically in Figure 2.

The release of FFA from fat depots is variable, with decreases in their serum values reported in some studies[12,24,33,34,51,52] and increases in others.[22,53-59] Nevertheless, the fatty acids continue to serve as a primary source of metabolizable energy for most body cells. Despite any changes in their plasma concentration, the movement of FFA into the liver continues.[51] Within the liver, FFA are incorporated into triglycerides, sometimes at an accelerated rate.[39,40,51,59] Hepatic production of triglycerides contributes to infection-induced hyperlipidemia as does an impairment in triglyceride disposal mechanisms.[58,59] In addition, droplets of lipid begin to accumulate within hepatic cells during sepsis, giving rise to histological changes characteristic of fatty metamorphosis throughout the liver.[53,54,57]

Guckian[39] found a decrease in the oxidation of acetate by liver slices from rabbits with induced pneumococcal infection, and an increase in acetate incorporation into lipids. Fiser et al[51] found an increase in the rate of fatty acid uptake by the liver in monkeys with induced endotoxemia, along with an accelerated formation of triglycerides from fatty acids.

Although peripheral cells can oxidize ketones during infection, an inhibition of ketone body production accompanies the changes in hepatic fat metabolism.[33,34] Ketone synthesis is known to take place within the mitochondria as diagrammed schematically in Figure 3. Its inhibition during infection could be due, in theory, to any one of several causal mechanisms, or to a combination of these mechanisms.

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These possibilities include: 1) high plasma insulin values; 2) a deficiency of hepatic carnitine, since carnitine is required to permit the transport of long-chain FFA into the mitochondria in the form of fatty acylcarnitines; 3) a failure of electron transport systems within the mitochondria; 4) a physiochemical disruption of mitochondrial functions; 5) a failure of beta-odixation mechanisms within the mitochondria, since these are necessary for splitting off the acetyl-CoA precursors of ketone bodies from long-chain or short-chain fatty acyl-CoA molecules; 6) an inhibition of ketogenic enzymes; and 7) the inhibiting effect on ketogenesis of ongoing fatty acid synthesis within the liver.

A precursor of fatty acid synthesis, malonyl-CoA, has recently been postulated by McGarry et al[60] to inhibit ketogenesis by interfering with the formation and transport into the mitochondria of long-chain fatty acylcarnitine molecules. In concept, malonyl-CoA could serve as an internal regulator within hepatic cells to turn off ketone production whenever the liver cells became engaged in synthesizing new fatty acid molecules. Fatty acid synthesis is not simply a reversal of fatty acid degradation but involves a distinctly different pathway which functions in the cytosol rather than in the mitochondrial matrix. Fatty acid synthesis starts with the carboxylation of acetyl-CoA to malonyl-CoA. This is an irreversible step, requiring acetyl-CoA, bicarbonate, ATP and the catalytic action of acetyl-CoA carboxylase. This step occurs in two stages, the first of which requires formation of a carboxybiotin intermediate. Fatty acid synthesis then proceeds by the addition to

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malonyl-CoA of 2-carbon units obtained from acetyl-CoA.

Although hepatic concentrations of malonyl-CoA have not been measured during sepsis, the accumulation of lipid droplets in hepatic cells and of triglycerides in serum would both suggest that fatty acids are being synthesized and that some regulatory intermediary such as malonyl-CoA could be accumulating in quantities sufficient to inhibit ketogenesis.

Neufeld and coworkers[33-34] were unable to detect any disturbance in mitochondrial electron transport, in beta-oxidation function of the TCA cycle, or in acetoacetate formation that could account for inhibited ketogenesis during sepsis. Similarly, Pace and her colleagues[61] found no decline in the hepatic content of free or esterified carnitine during the course of experimentally induced pneumococcal infection in laboratory rats. However, there was an increase in hepatic short-chain acylcarnitines and a decrease in hepatic long-chain acylcarnitines during this model infection. Pace et al[61] found, in addition, that perfused livers from septic animals had a decreased capacity to produce ketones from long-chain fatty acids or to oxidize them. Canonico et al[40] studied lipid metabolism in isolated hepatic cells obtained from rats with pneumococcal sepsis. When these hepatocytes were studied in vitro using [^{14}C]acetate, they showed an increased capacity to synthesize various lipids. In comparison to control values, there was an 18-fold increase in the production of cholesterol and diglycerides, a 5-fold increase in triglycerides and a 6-fold increase in fatty acids. In contrast, these isolated hepatocytes

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from septic rats showed a 27% decrease in ketone production and a similar decrease in their ability to oxidize [^{14}C]acetate to $^{14}CO_2$. These findings suggested that the increased flow of acetyl-CoA moved toward the synthesis of new fatty acids rather than toward ketogenesis. This finding would support the concept that ongoing hepatic lipogenesis will inhibit hepatic ketogenesis. This mechanism should prevent both fatty acids and ketones from being produced concomitantly.

Since ketogenesis takes place in the mitochondria, Canonico et al[40-42] postulated that physical abnormalities in mitochondrial structure might be responsible for the observed inhibition of ketogenesis rather than some biochemical pathway defect. This possibility was supported by data suggesting that the normally narrow equilibrium density range of hepatic metochondria was considerably broadened during sepsis. However, in contrast to studies performed in perfused livers using fatty acids,[61] mitochondria obtained from the livers of infected rats appear capable of oxidizing palmityl-carnitine at the same rate as hepatic mitochondria from fasted control rats.[34]

The importance of insulin in helping to account for suppressed ketogenesis has now been clearly shown by Neufeld et al.[62] Rats with experimentally induced pneumococcal sepsis either failed to develop ketosis, or they failed to remain ketotic if starvation-induced ketosis had been initiated prior to the infection. In marked contrast, rats that lacked an ability to produce insulin (because of streptozoticin-induced diabetes) demonstrated no impairment of ketogenesis when

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similarly infected. However, the rate of ketogenesis in these diabetic insulinopenic rats was so high that it may have masked possible inhibitory effects due to infection-induced mechanisms other than high insulin values.

Not all studies have found an excess pancreatic secretion of insulin during infection. Some of the differences between studies can possibly be explained by the type of infection, the use of bacterial endotoxin, the species of animal, the time of study in relation to the severity of the disease, or to the use of glucose infusions to stimulate insulin release from the pancreas. Greater-than-normal increases in serum insulin values have generally been observed when glucose infusions were given. Similar post-glucose increases have been reported during infections or endotoxemia in monkeys[13,23] and during endotoxemia in dogs.[16] In contrast, baboons with Escherichia coli sepsis have exhibited fasting hypoinsulinemia and a blunted insulin response to infused glucose.[63] The severity of hypoinsulinemia in these baboons correlated with the severity of the infection as judged by survival time and was attributed to an inhibition of insulin secretion by circulating alpha-adrenergic hormones.[64]

The inhibition of ketogenesis during sepsis may, in part, be ascribed primarily to the actions of insulin which is secreted during infection by the pancreatic islet beta-cells. The antiketogenic effect of insulin would seem to result from its lipogenic actions on hepatic cells as well as on adipocytes.

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Conclusions

Acute febrile infections in the normally nourished host produce a hypermetabolic state accompanied by the need to generate sufficient energy-yielding substrates to meet the demands of various body cells. The mechanisms used to produce these substrates during acute infection differ markedly from those employed to sustain the body during periods of simple starvation.

Acute sepsis is characterized by an accelerated catabolism of somatic proteins, an increased rate of oxidation and transamination of branched-chain amino acids within muscle, an enhanced formation of lactic acid, alanine and glutamine in muscle, an enhanced flux of these substrates from muscle to liver, and an acceleration of the synthesis and release of glucose from the liver. Endocrine responses which influence these metabolic changes include an enhanced secretion of both insulin and glucagon from pancreatic islet cells and a resultant decrease in the molar ratio of insulin to glucagon in plasma. The secretion of the adrenal glucocorticoids and growth hormone are increased as may be the secrection of catecholamines.

The accelerated release of glucose from the liver is generally accompanied by an increase in the glucose pool size and an increase in the rate of glucose utilization as a cellular fuel. This is especially true for the phagocytic cells during pyogenic infections. The increased utilization of amino acids as a substrate for hepatic gluconeogenesis provides the excess amino nitrogen groups used by the liver for

ureagenesis which is also accelerated when acute infection develops in a normally nourished host.

The hormonal, enzymatic, and substrate interrelationships within the liver combine in their effects to inhibit ketogenesis and stimulate hepatic lipogenesis during acute sepsis.

While acceleration of gluconeogenesis and ureagenesis and an inhibition of ketogenesis seem to characterize the host response to acute sepsis, these responses as well as the hormonal ones may be modified or abolished if infection develops in a poorly nourished host, in the presence of complicating trauma or other diaseses, or whenever the infectious process itself becomes overwhelmingly severe.

Questions have been raised about the possible benefits to the host, or the harmful effects of fever[65] and of anorexia.[66] Hopefully the new insights concerning energy-generating mechanisms in the infected host can now be studied in experimental animals and man to identify those nutritional forms of supportive therapy which are optimally beneficial. Of major concern are the extensive losses of body protein, and the harmful effects on host defensive mechanisms.

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<u>Illustrations</u>

Figure 1. Gluconeogenesis during sepsis. This is a schematic representation of metabolic and hormonal aspects of the gluconeogenic response during early sepsis (right) and its contrast to the normal adaptive responses to simple starvation (right). During simple starvation, the mobilization of fat and the ketogenic response provide energy-yielding substrates which allow for the conservation of body protein and amino acids. In contrast, body proteins are catabolized at an accelerated rate during sepsis, gluconeogenesis is stimulated, insulin and the gluconeogenic hormones are secreted in excess, ketogenesis is inhibited, and body fat stores are not promptly mobilized. Heavy arrows indicate enhanced responses.

Figure 2. Lipid metabolism during infection. This is a schematic representation of normal pathways of lipid metabolism (left) and the changes observed during some acute infections (right). Accentuated pathways represent increased rates, dashed pathways represent diminished rates, and vertical arrows to the right of lipid designations represent changes in the plasma concentration of the lipid.

Figure 3. Ketogenesis during sepsis. This is a schematic representation of a hepatocyte and its mitochondria during simple starvation (left) and during acute sepsis (right). Accentuated arrows represent increases and dashed arrows represent decreases.
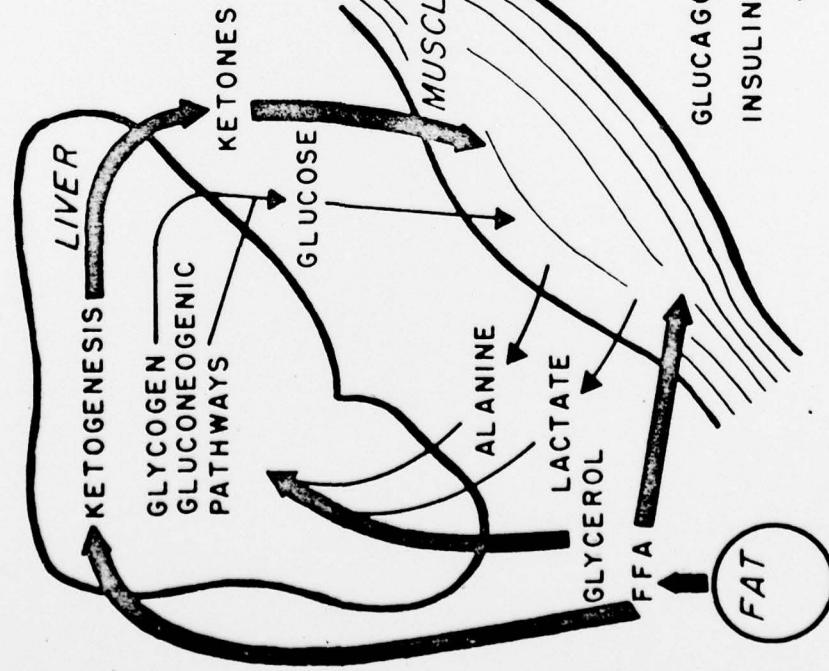
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Table 1

Important Early Historical Events[1,2]

1835	Graves	Advocated oral diet therapy for patients with fevers.
1857	Parkes	Showed an increased loss of body nitrogen during typhus.
1871	Liebermeister	Measured increased CO_2 exhalation during malarial fevers.
1882	von Hosslin	Advocated a liberal diet during fevers.
1895	Voit	Demonstrated that increased dietary carbohydrate could "spare" body protein during endotoxin fever in dogs.
1909	Shaffer and Coleman	Demonstrated "protein-sparing" effects of carbohydrate feedings in typhoid fever.
1920's	Columbia University Group (DuBois, McCann, Barr, Cecil, Coleman)	Performed whole body calorimetry during tuberculosis, erysipelas, typhoid fever, malaria, and pneumonia.

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Table 2

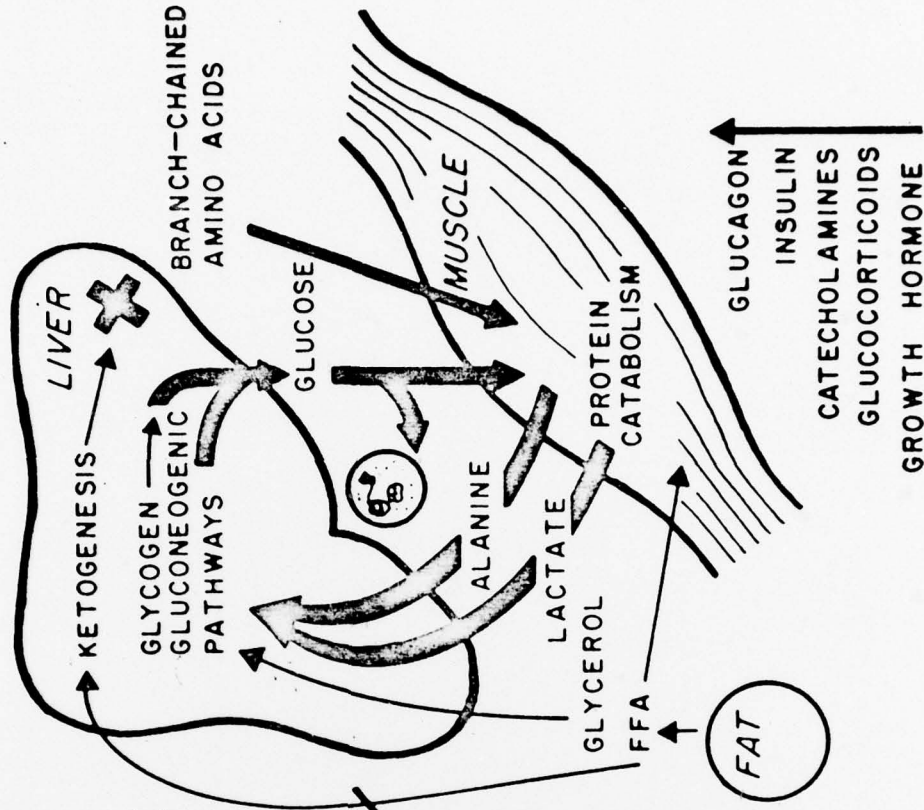Gluconeogenesis in septic patients (from C. L. Long[5])

| | (^{14}C) Glucose Data | | | L-(^{14}C) Alanine Data | |
	Turnover Rate mg/min	Oxidation Rate mg/min	Pool Size g	Appearance in Glucose % of dose	Oxidation to CO_2 in 3 hr % of dose
Normal	152	85	17.8	11.1	28.7
Major Injury and Sepsis	310	181	49.7	—	—
Severe Sepsis	—	—	—	23.1	31.9

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NORMAL—STARVATION—ADAPTED

SEPSIS

NORMAL

INFECTED
(ACUTE)

FAT DEPOT

LIVER

HSL

TG

FFA
(COMPLEX
WITH
ALBUMIN)

GLYCEROL

TG

KETONES

LP-TG

LPL

PL
C

AcCoA $\longrightarrow$ CO_2
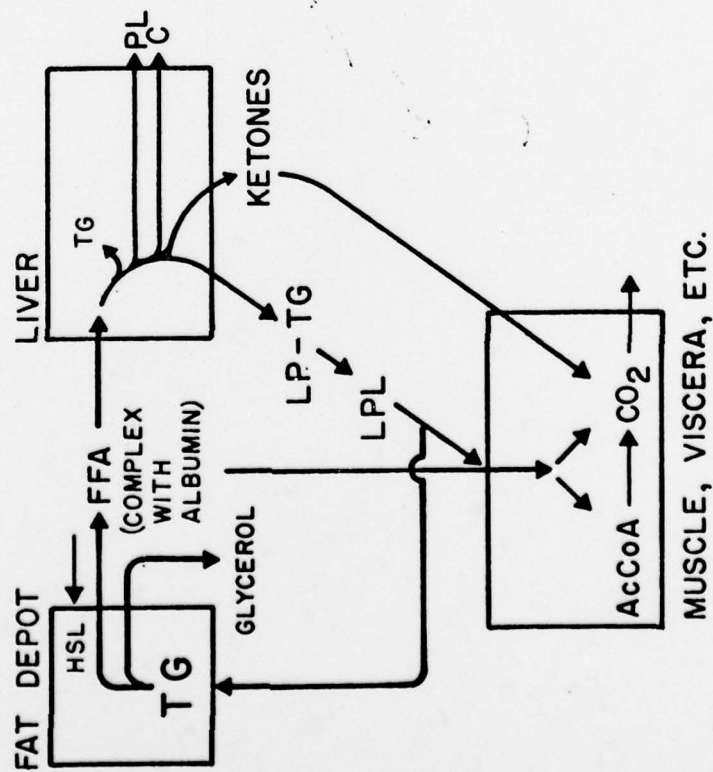
MUSCLE, VISCERA, ETC.
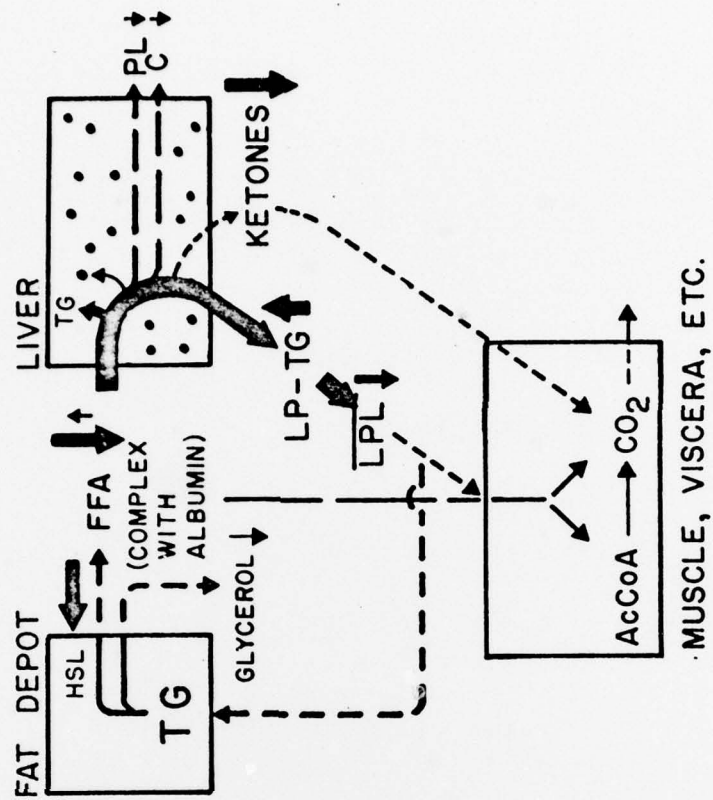
FFA = FREE FATTY ACIDS
TG = TRIGLYCERIDES
C = CHOLESTEROL

HSL = HORMONE-SENSITIVE LIPASE
LP = LIPOPROTEIN
PL = PHOSPHOLIPID

LPL = LIPOPROTEIN LIPASE
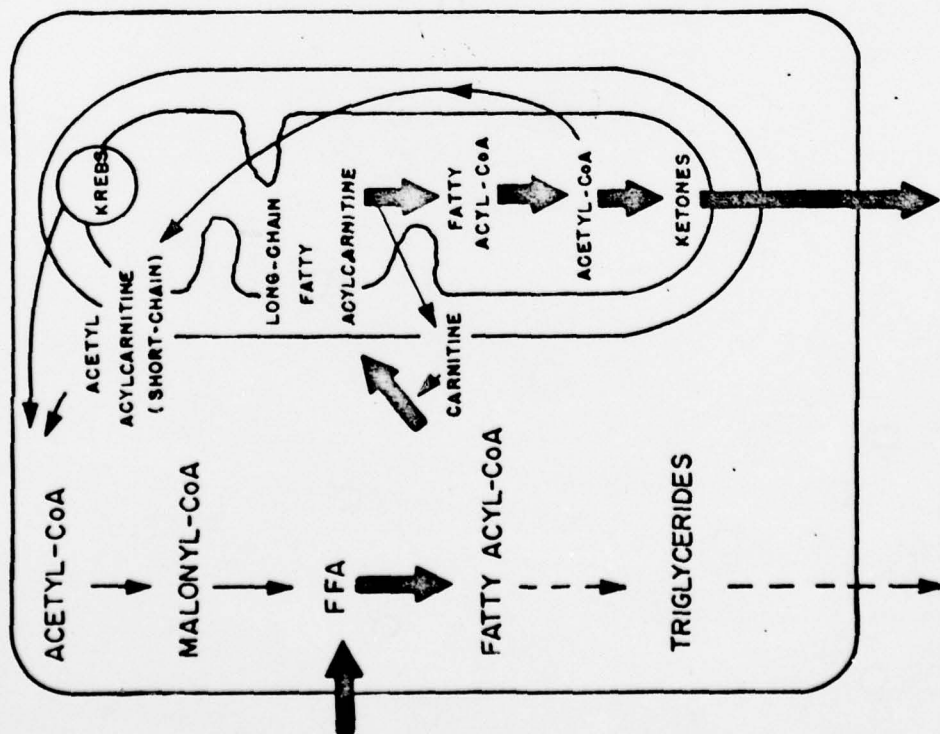(ALSO CALLED PHLA)
= FAT DROPLETS

HEPATOCYTE – SEPTIC HOST

HEPATOCYTE – FASTING NORMAL